Docket No.: 532512000401
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gregory M. LANZA et al.

Application No.: 10/620,725

Filed: July 15, 2003

For: LIGAND-TARGETED EMULSIONS CARRYING BIOACTIVE AGENTS

Confirmation No.: 1157

Art Unit: 1615

Examiner: David L. Vanik, Ph. D.

DECLARATION OF GREGORY M. LANZA

Commissioner for Patents
P.O. Box 1450
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Dear Sir:

I, Gregory M. Lanza, declare as follows:

1. I am a co-inventor of the subject matter described in the above-referenced application. I have been working with targeted fluorocarbon nanoparticles as drug delivery carriers and as imaging agents for over a decade. A copy of my *curriculum vitae* is attached.

2. I prepared the compositions of doxorubicin and paclitaxel described in Examples 1-2 and 4 of the present application, as well as a similar composition containing rapamycin. In all cases, the drug is mixed with initial ingredients in a solvent such as chloroform and evaporated to a film prior to forming the nanoparticles, rather than added at a later time in the preparation.

3. Doxorubicin, supplied as the hydrochloride, is highly water-soluble. Doxorubicin-loaded nanoparticles, where the doxorubicin is not incorporated into the solvent film prior to preparation of the particles, is either not incorporated into, or rapidly released out of, the lipid/surfactant layer.

4. Paclitaxel is very insoluble in water and adding the drug to water leads to crystalline precipitation. If ethanol is added, the emulsion is cracked or destroyed. However, following the procedure of the present application - i.e. mixing in solvent with ingredients of the lipid/surfactant layer and evaporating prior to forming the nanoparticles, it can be successfully included and retained in the lipid/surfactant layer.

5. I have done similar experiments with rapamycin, which is also poorly soluble in water. By following the procedures outlined in the present application, stable loading of the drug in the lipid/surfactant layer is achieved.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at San Diego, California, on 25 October 2006.

Gregory M. Lanza

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007-54-0672

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Present Position:

Associate Professor of Medicine
Adjunct Associate Professor of Biomedical Engineering

Education:

1975: Bachelor of Arts
Colby College
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1978: Masters of Science
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University of Georgia
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1981: Doctor of Philosophy
Department of Poultry Science
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1992: Doctor of Medicine
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Academic Positions/Employment:

9/04-Present	Adjunct Associate Professor of Biomedical Engineering Washington University Medical Center St. Louis, Missouri 63110
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7/96-6/99:	Research Instructor of Medicine Washington University Medical Center St. Louis, Missouri 63110
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8/88-6/92:	Northwestern University Medical School 303 Chicago Avenue Chicago, Illinois
6/81-8/88:	Animal Sciences Division Monsanto Company 700 Chesterfield Parkway St. Louis, Missouri
1985-1988:	Product Biology Research Manager Budget: $2.9 Million/yr; Responsibility: Establish and direct a preclinical product development research program for dairy use of recombinant bovine somatotropin in support of US and ex-US regulatory approvals. The position was responsible for supporting the development and optimization of the product, designing, conducting and analyzing target and model animal pharmacodynamic

(efficacy and physiology), pharmacokinetic, safety (toxicology, clinical and anatomical pathology) and metabolism residue studies. Statistics and Quality Assurance groups were also created and managed between 1983 and 1988.

1984-1985: Senior Research Group Leader

1983-1984: Research Specialist

1981-1983: Senior Research Biologist

1976-1981: Department of Poultry Science
University of Georgia
Athens, Georgia 30602

Research at the MS and PhD levels focused on biochemically quantifying resistance/susceptibility of Gallus domesticus to aflatoxicosis and developing corresponding genetic selection programs.

1978: International Research in Greece

Responsibility: Provide consultation and conduct research in Greek agricultural environment concerning the incidence of tibial dyschondroplasia, an issue of international litigation between Voktas, Inc. and Central Soya, Inc. (P.I. Drs. Leo Jensen and Roland Leach).

Medical Licensure and Board Certification:

Diplomat of the National Board of Medical Examiners, Parts I, II and III
Missouri Medical License: #101080 (1993)
Diplomat of American Board of Internal Medicine, 11/95
Diplomat of American Board of Internal Medicine, Cardiology, 11/99
American Society of Echocardiography, Specialty Certification in Echocardiography, 6/1999

Honors and Awards:

Phi Kappa Phi Honor Society
Gamma Sigma Delta Agricultural Honor Society
Hubbard Farms Charitable Foundation Scholarship
Poultry Science Association Graduate Student Award
Northwestern University Medical Student Research Grant
NIH Research Festival for Outstanding PGY1 Researchers.
American Heart Association Fellowship, Missouri Affiliate (1995-1997)
Bristol-Myers Squibb Fellowship Award (1997)
Bracco Diagnostics Inc./Society for Cardiac Angiography and Interventions Fellowship (1998)
1998 ACC/Littmann Scholarship Award
American Heart Association, Missouri Affiliate – Beginning Grant (1999-2001)

American College of Cardiology, Searle Career Development Award (2000)
Barnes-Jewish Hospital Research Foundation Award (1999-2001)
NCI Unconventional Innovation Program Awards (2000-2003, 2002-2005,2003-2006)
NHLBI RO1 (2004-2008)

Professional Societies and Organizations:

Acoustic Society of America
American Association for the Advancement of Science
American Medical Association
Missouri Board of Healing Arts
American Heart Association
American College of Cardiologists
Society of Cardiovascular Magnetic Resonance
International Society for Magnetic Resonance in Medicine
American Society of Echocardiology
Society for Molecular Imaging

Research Support:

American Heart Association Fellowship, Missouri Affiliate (1995-1997): Principal Investigator
Barnes Jewish Hospital Foundation (1996-1997): $50,000, Principal Investigator
Bracco Diagnostics Inc./Society for Cardiac Angiography and Interventions Fellowship (1998-1999): $25,000, Principal Investigator
American Heart Association, Missouri Affiliate – Beginning Grant (1999-2000): $35,000/yr, Principal Investigator
Barnes Jewish Hospital Foundation (1999-2000): $50,000, Principal Investigator
American College of Cardiology Searle Award in Cardiovascular Disease (2000) $40,000, Principal Investigator
National Cancer Institute (2000-2003): $2,092,153, Principal Investigator
Barnes Jewish Hospital Foundation (2000-2001): $40,000, Principal Investigator
National Cancer Institute (2002-2005): $2,782,905, Principal Investigator
National cancer Institute (2003-2006): $5,097,055, Principal Investigator
National Health Lung and Blood Institute (2004-2008): ~$1,000,000, Principle Investigator

Issued US Patents (> 25 Pending):

1. DeGeeter M J, **Lanza GM**, Vineyard BD. Composition and method for improving feed utilization or tissue production in animals. 10/21/1986, Monsanto Company. US Pat. No. 4,618,604. EEC Pat No. EP00139624B1, 04/15/1987.

2. DeGeeter M J, **Lanza GM**. Method for improved bovine milk production.
08/03/1983, Monsanto Company. EEC Pat No. EP00085036A1.

3. **Lanza GM**, Alkan MH, Klegerman ME, Vonesh MJ, McPherson DD. Acoustically reflective liposomes and methods to make and use the same. 03/18/1997, Northwestern University, US Pat. No:5,612057.

4. **Lanza GM,** Wickline SA. Avidin-Biotin conjugated emulsions as a site specific binding system. 11/25/1997, Barnes-Jewish Hospital. US Pat. No. 5,690,907.

5. **Lanza GM,** Wickline SA. Method of MRI using avidin-biotin conjugated emulsions as a site specific binding system. 07/14/1998, Barnes-Jewish Hospital. US Pat No. 5,780,010.

6. **Lanza GM,** Alkan-Onyuksel MH, Klegerman ME, Vonesh MJ, McPherson DD, Kane BJ, Murer SE. Acoustically reflective liposomes and methods to make and use the same. 01/12/1999, Northwestern University. US Pat No. 5,858,399.

7. **Lanza GM,** Wickline SA. Site specific binding system, imaging compositions and methods. 11/23/1999, Barnes-Jewish Hospital. US Pat No. 5,989,520.

8. **Lanza GM,** Wickline SA. Site specific binding system, nuclear imaging compositions and methods. 09/28/1999, Barnes-Jewish Hospital. US Pat No. 5,958,371.

9. **Lanza GM,** Wickline SA. Site specific binding system, imaging compositions and methods. 11/23/1999, Barnes-Jewish Hospital. US Pat No.6,548,046.

10. **Lanza GM,** Wickline SA. Ligand-targeted emulsions carrying biocactive agents. October 28, 2000. US Patent 6,676,963.

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1. **Lanza GM,** Washburn KW, Wyatt RD, Edward HM Jr. Depressed Fe-59 absorption due to dietary aflatoxin. *Poultry Sci* 1979; 58:1439-1444.

2. **Lanza GM,** Washburn KW, Wyatt RD. Variation with age in response of broilers to aflatoxin. *Poultry Sci* 1980; 59: 282-288.

3. Stewart RG, Wyatt RD, **Lanza GM,** Edwards HM Jr, Ruff MD. Physiological effects of Gentian violet on broiler chickens. *Poultry Sci* 1980; 59: 234- 239.

4. **Lanza GM,** Washburn KW, Wyatt RD. Strain variation in hematological response of broilers to dietary aflatoxin. *Poultry Sci* 1980; 59: 2686-2691.

5. Washburn KW, Maeda Y, **Lanza GM.** Protein polymorphisms in a randombred chicken population. *Anim Blood Groups and Biochem Gen* 1980; 11: 261-269.

6. **Lanza GM,** Washburn KW, Wyatt RD. Time-course analysis of chick (Gallus domesticus) response during aflatoxicosis. *Toxicon* 1980; 19: 563-566.

7. **Lanza GM,** Washburn KW, Wyatt RD. Effect of linoleic acid on broilers to graded levels of aflatoxin. *Arch Geflugelk* 1981; 45: 206-211.

8. **Lanza GM,** Washburn KW, Wyatt RD, Edwards HM Jr. Strain variation in Fe-59 absorption during aflatoxicosis. *Poultry Sci* 1981; 60: 500-504.

9. **Lanza GM,** Washburn KW, Wyatt RD, Marks HL. Genetic variation of physiological response to aflatoxin in Gallus domesticus. *Theor and Appl Genet* 1981; 63: 207-212.

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13. Washburn KW, Wyatt RD, Potts PL, **Lanza GM.** Effects and mechanism of aflatoxin variation in shell strength. *Poultry Sci* 1985; 64: 1302-1305.

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83. Morawski AM, Winter PM, Caruthers SD, Abendschein D, Fuhrhop RF, Scott MJ, Crowder KC, **Lanza GM**, Wickline SA. Sensitive detection of tissue-factor protein expressed on vascular smooth muscle cells with ligand-targeted paramagnetic nanoparticles at 1.5 Tesla. Mol Imaging 2003 2: 279.

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85. Winter PM, Athey PS, Kiefer GE, Gulyas G, Fuhrhop RF, Robertson JD, Wickline SA, **Lanza GM**. Improved paramagnetic chelate for molecular imaging with MRI. Contrast Media Research Symposium, San Diego, CA, October, 2003 (In press)

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87. Winter PM, Caruthers SD, Harris TD, Schmeider AH, Abendschein D, Cyrus T, Fuhrhop RF, Dietz EK, Williams TA, Allen JS, Zhang H, Wickline SA, **Lanza GM**. Molecular imaging of avb3-integrin: an opportune biochemical signature for

oncologic and cardiovascular diseases. Contrast Media Research Symposium, San Diego, CA, October, 2003 (In Press)

88. Winter PM, Morawski AM, Caruthers SD, Harris TD, Allen JS, Zhang H, Fuhrhop RF, Lacy EK, Williams TA, **Lanza GM**, Wickline SA. Specific molecular imaging of vasa vasorum in early atherosclerosis with avb3-integrin targeted nanoparticles. *Circulation* 108;168.

89. Morawski AM, Winter PM, Abendschein D, Caruthers SD, Fuhrhop RF, Scott MJ, Crowder KC, **Lanza GM**, Wickline SA. Magnetic resonance immunocytochemistry: characterization of tissue-factor expression by smooth muscle cells with targeted paramagnetic nanoparticles. Circulation 2003; 108:139.

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Chapters:

1. **Lanza GM**, Wallace KD, Miller JG, Wickline SA. Development of a novel site targeted ultrasonic contrast agent. In: Advances in Echo Imaging Using Contrast Enhancement. N.C. Nanda, R. Schlief, and G.G. Goldberg, editors. Kluwer Academic Publishers, Norwell, MA. 1997, pp. 655-667.

2. Wickline SA, Miller J, **Lanza G**. Quantitative ultrasonic tissue characterization with intravascular and transcutaneous ultrasound. In: Non-invasive Imaging of Atherosclerosis. M. Mercuri, D.D. McPherson, H. Bassiouny, S. Glagov, editors. Kluwer Academic Publishers, Norwell, MA. 1998, pp 169-188.

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4. **Lanza GM**, Caruthers SD, Wickline SA: Molecular Imaging. *In* MRI of the Cardiovascular System, ed Lardo, Fayad, Chronos and Fuster. Martin Dunitz Ltd. London (In press)

5. Tillman C, Winter PW, Wickline SA, **Lanza GM**: Nanoparticle formulations for cardiac magnetic resonance imaging. *Expert Review of Cardiovascular Therapy* (In press)

6. Winter PM, Caruthers SD, Wickline SA, **Lanza GM**: Nanotechnologies for Cellular and Molecular Imaging by MRI, In "Nanofabrication Towards

biomedical Applications" (C Kumar, J Hormes, C Leuschner Eds.), Wiley-VCH (in review)

7. Targeted MRI Contrast Agents In Magnetic Resonance Imaging: Methods and Biological Applications SD Caruthers, PM. Winter, SA. Wickline and GM. Lanza. (In Press)

Invited Presentations (since 1997)

1. Invited Speaker: Contrast Media Research, Kyoto, Japan, 5/97 - Enhanced detection of thrombi with a novel fibrin targeted magnetic resonance imaging agent.

2. Invited Speaker: Nycomed Imaging, Inc, Oslo, Norway, 6/97 - Review of targeted contrast applications for ultrasonic imaging.

3. Invited Speaker: NIH Seminar, Washington, DC, 9/97 - A novel targeted contrast agent for ultrasonic and magnetic resonance imaging.

4. Invited Speaker: Abbott, Inc, Chicago, IL, 10/97 - Review of targeted contrast technology for ultrasonic and MRI imaging.

5. Invited Speaker: Imclone Systems, Inc, Chicago, IL, 2/98 - Review of targeted contrast technology for ultrasonic and MRI imaging.

6. Invited Speaker: Acoustic Society of America, Seattle, WA 5/98 - Targeted acoustic contrast agents: new opportunities for ultrasound in medical diagnosis and therapy.

7. Invited Speaker: Abbott, Inc, Chicago, IL, 12/99- Updated review of targeted contrast technology for ultrasonic and MRI imaging.

8. Invited Speaker: WU Biochemical Engineering Seminar 12/99 - Molecular Imaging with Ligand-Targeted Immunoemulsions.

9. Invited Speaker: Schering AG, Inc, Berlin, Germany 5/2000- Updated review of targeted contrast technology for ultrasonic and MRI imaging.

10. Invited Speaker: Allerton Conference, Acoustic Contrast Agents, Allerton, Illinois 6/2000- Targeted acoustic contrast agents: new opportunities for ultrasound in medical diagnosis and therapy.

11. Invited Speaker: FMC Technology Review –2000, Princeton, NJ 9/2000 – Angiogenesis and Wound Healing

12. Invited Speaker: Imaging in 2020 (NCI) – 9/2001 – "Molecular Imaging and Targeted Drug Delivery with a Novel Perfluorcarbon Nanoparticle"

13. Invited Speaker: CMR 2001, 10/2001 Capri, Italy – "Molecular Imaging and Targeted Drug Delivery with a Novel, Ligand-Directed Paramagnetic Nanoparticle Technology"

14. Invited Speaker: International Society for BioMEMS and Biomedical Nanotechnology 9/2001, Columbus, OH – "Magnetic Resonance Molecular Imaging and Targeted Drug Delivery with Site-specific Nanoparticles"

15. Invited Speaker: NCI Unconventional Innovative Projects Program – Washington, DC - 2/2002 – "Molecular Imaging and Local Drug Delivery With a Novel AvB3-Targeted Nanoparticle Emulsion for Noninvasive Detection and Treatment of Cancer"

16. Invited Speaker: Vulnerable Plaque Symposium 3/2002 Atlanta, GA "MR Imaging of Fibrin to Detect Plaque Mural Thrombi "

17. Invited Speaker: Saint Louis University Cardiology Seminar Series 5/2002 St. Louis, MO – ""Molecular Imaging and Targeted Therapy"

18. Invited Speaker: Molecular Imaging Workshop 6/2002 Helsinki, Finland "Molecular Imaging and Targeted Therapy"

19. Invited Speaker: Joint NASA-NCI Biomolecular Physics and Chemistry Program – Monterey, CA - 7/2002 – "Unconventional Innovative Projects Lessons Learned"

20. Invited Speaker: NCI Unconventional Innovative Projects Program – San Diego, CA - 2/2003 – "Molecular Imaging and Local Drug Delivery With a Novel AvB3-Targeted Nanoparticle Emulsion for Noninvasive Detection and Treatment of Cancer Update"

21. Invited Speaker Seminar- Johns Hopkins Medical School - Department of Radiology 5/2003. Molecular Imaging and Targeted Drug Therapy.

22. Invited Speaker: Small Talk 2003. Molecular Imaging and Targeted Drug Delivery: Emerging Medical Paradigms

23. Invited Speaker: American Chemical Society 2003. New York, NY. September, 2003. Molecular imaging and targeted drug therapy: merging paradigms in medicine.

24. Invited Speaker: IEEE -UFFC. Honolulu, HI. October 2003. Molecular imaging and targeted drug delivery: merging medical paradigms

25. Invited Speaker: Northwestern Echo 2003. Chicago, IL, October 2003. Molecular Imaging.

26. Invited Speaker: AHA-Sunday Sessions. Orlando, FL. November, 2003 Molecular imaging and therapy; new paradigms for 21st century medicine.

27. Invited Speaker Society of Cardiac MRI. Barcelona, Spain February 2004. State of the Art in Molecular Imaging and Targeted Therapeutics.

28. Invited Speaker: 5th Magnetic Microsphere Meeting Scientific and Clinical Applications of Magnetic Carriers. May, 2004. Lyon, France Molecular Imaging

& Targeted Drug Delivery with a Site-specific Nanoparticle PlatformTechnology Emerging Opportunities for Non-invasive Diagnosis and Image-augmented Therapy

29. Invited Speaker: International Symposium on Therapeutic Ultrasound. Kyoto, Japan, September, 2004. Molecular Imaging &Targeted Drug Delivery with a Site-specific Nanoparticle PlatformTechnology Emerging Opportunities for Non-invasive Diagnosis and Image-augmented Therapy

30. Invited Speaker: 8th Annual Heart Failure Society of America. Toronto, Canada, September 2004. Targeted Imaging and Therapeutics

31. Invited Speaker: Gordon Research Conference. Waterville, Maine. June, 2004. Metals Meddle in Medicine.

32. Invited Speaker. Magnetic Nanoparticle Research Symposium, Baton Rouge, LA, June, 2004. Molecular Imaging &Targeted Drug Delivery with a Site-specific Nanoparticle PlatformTechnology Emerging Opportunities for Non-invasive Diagnosis and Image-augmented Therapy

33. Invited Speaker: Evanston Hospital/Northwestern University Medical School. March, 2004. Ligand-Directed Nanoparticles in Molecular Medicine: Emerging Opportunities

34. Invited Speaker: Society of Vascular Surgery/NHLBI Joint Workshop March, 2004, Bethesda, MD. Targeted Imaging and Therapeutics.

35. Invited Speaker. ISMRM Workshop on MR in Drug Development, McLean, VA April, 2004 MR Nanoparticles Technology Drug Development for Atherosclerosis

36. Invited Speaker. American Society of Nuclear Cardiology. May, 2004, Bethesda, MD, Combined Therapeutic and Molecular Imaging Agent for Treatment and Monitoring of Plaque Angiogenesis in Atherosclerosis

37. Invited Speaker. American Society of Nuclear Cardiology. May, 2004, Bethesda, MD, Nanotechnology and Molecular Imaging in Atherosclerosis

38. Invited Speaker: Invited Speaker. AHA; Atherosclerosis, Thrombosis, and Vascular Biology. San Francisco, CA May, 2004, Bethesda, MD, Combined Therapeutic and Molecular Imaging Agent for Treatment and Monitoring of Plaque Angiogenesis in Atherosclerosis

39. Invited Speaker. Philips Medical Systems Molecular Imaging Users Group. September, 2004. Saint Louis, MO. Perfluorocarbon nanoparticles: a multimodal platform for targeted therapy and Molecular Imaging.

40. Invited Speaker: University of Virginia Cardiology Grand Rounds. Charlottesville, VA. September, 2004. Emerging Molecular Imaging and Targeted Therapy Opportunities

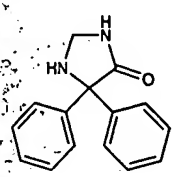
41. Invited Speaker: University of Nebraska First Annual Biomagnetism Symposium. Lincoln, Nebraska, October, 2004 A Personalized Nanotechnology Approach to Cardiovascular Disease

42. Invited Speaker: WU/Pfizer Retreat on Cardiovascular Disease October, 2004. A Personalized Nanotechnology Approach to Cardiovascular Disease.

43. Invited Speaker: NCI Nanotechnology Conference: Overcoming Barriers to Collaboration. Cleveland, OH, October 2004. Development of Personalized Nanotechnology Approaches to Oncologic Disease

44. Invited Speaker: University of Miami, Department of Medicine and Division of Cardiology Grand Rounds. December, 2004.

diphenylglyoxaline; SKF-2599; Glior. $C_{15}H_{14}N_2O$; mol wt 238.29. C 75.61%, H 5.92%, N 11.76%, O 6.71%. Prepd by reduction of diphenylthiohydantoin with sodium: Biltz, Seydel, *Ann.* 391, 218 (1912); with Raney nickel: Whalley *et al., J. Am. Chem. Soc.* 77, 745 (1955); Goodman, U.S. pat. 2,744,852 (1956).

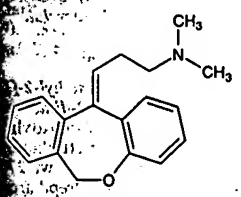


Stout plates from methanol, mp 183° (Goodman); crystals from alc, mp 185.5-186.5° (Biltz). Moderately sol in glacial acetic acid; less sol in alc, ethyl acetate, benzene, chloroform. Practically insol in water, ligroin.

Hydrochloride, $C_{15}H_{14}N_2O.HCl$, dec 205-206°.

THERAP CAT: Anticonvulsant.

3492. Doxepin. *3-Dibenz[b,e]oxepin-11(6H)-ylidene-N,N-dimethyl-1-propanamine; N,N-dimethyldibenz[b,e]oxepin-11(6H)-propylamine;* 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin; P-3693A. $C_{19}H_{21}NO$; mol wt 279.38. C 81.68%, H 7.58%, N 5.01%, O 5.73%. Prepn of mixture of *cis*- and *trans*-isomers: K. Stach, F. Bickelhaupt, *Monatsh.* 93, 896 (1962); F. Bickelhaupt *et al., ibid.* 95, 485 (1964); Neth. pat. Appl. 6,407,758; K. Stach, U.S. pat. 3,438,981 (1965, 1969 both to Boehringer Mann.); and separation and activity of isomers: B. M. Bloom, J. R. Treiter, Belg. pat. 641,498; *eidem*, U.S. pat. 3,420,851 (1964, 1969 both to Pfizer). Pharmacology: A. Ribbentrop, W. Schaumann, *Arzneimittel-Forsch.* 15, 863 (1965). Metabolism in animals: D. C. Hobbs, *Biochem. Pharmacol.* 18, 1941 (1969). Determn in plasma by GC/MS: T. P. Davis *et al., J. Chromatog.* 273, 436 (1983); by HPLC: T. Emm, H. J. Lesko, *ibid.* 419, 445 (1987). Clinical study in depression: K. Rickels *et al., Arch. Gen. Psychiat.* 42, 134 (1985). Comparative clinical trial with cimetidine, *q.v.*, in treatment of ulcers: R. K. Shrivastava *et al., Clin. Ther.* 7, 181 (1985). Review of pharmacology and therapeutic efficacy: R. M. Pinder *et al., Drugs* 13, 161 (1977).



Oily liq consisting of a mixture of *cis*- and *trans*-isomers. Hydrochloride, mp 154-157°, bp$_{0.2}$ 260-270°. LD_{50} in mice, rats (mg/kg): 1000 i.v.; 79, 182 i.p.; 135, 147 orally (Ribbentrop, Schaumann).

Hydrochloride, $C_{19}H_{21}NO.HCl$, *Adapin, Aponal, Curatin, Quitaxon, Sinequan.* Crystals, mp 184-186°, 188-189°. (A *trans* mixture of approx 1:5).

Maleate, crystals, mp 161-164°, 168-169°.

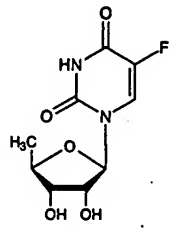
trans-Form hydrochloride, mp 192-193°.

cis-Form hydrochloride, *cidoxepin hydrochloride, P-4599.* Crystals, mp 209-210.5°.

THERAP CAT: Antidepressant.

THERAP CAT (VET): Antipruritic.

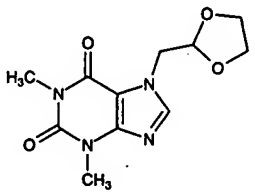
3493. Doxifluridine. *5'-Deoxy-5-fluorouridine;* 1-(β-D-2-deoxyribofuranosyl)-5-fluorouracil; 5'-DFUR; 5'-dFUrd; ftorafur; FT-207; NSC-19788; Flutron; Furtulon. $C_9H_{11}FN_2O_5$; mol wt 246.20. C 43.91%, H 4.50%, F 7.72%, N 11.38%, O 32.49%. Fluorinated pyrimidine nucleoside with cytostatic activity. Prepn: A. F. Cook, U.S. pat. 4,071,680 (1978 to Hoffmann-La Roche); H. Hrebabecky, J. Beranek, *Nucleic Acids Res.* 7, 1029 (1979); A. F. Cook *et al., J. Med. Chem.* 22, 1330 (1979). Stereospecific synthesis: J. Kiss *et al., Helv. Chim. Acta* 65, 1522 (1982). Mechanism of action studies: H.-R. Brunmann, A. Matter, *Cancer Res.* 42, 2412 (1982); R. D. Armstrong *et al., Cancer Chemother. Pharmacol.* 11, 102 (1983). Kinetics and metabolism in humans: J.-P. Sommadossi *et al., Cancer Res.* 43, 930 (1983). Clinical trials in colorectal carcinoma: R. Abele *et al., J. Clin. Oncol.* 1, 750 (1983); S. D. Fossa *et al., Cancer Chemother. Pharmacol.* 15, 161 (1985). Series of articles on animal toxicology: *Yakuri to Chiryo* 13, Suppl. 2, 221-430 (1985); acute toxicity: M. Shimizu *et al., ibid.* 209, *C.A.* 104, 14673z-14678e (1986). Evaluation of neurotoxicity in humans: M. S. Heier, S. D. Fossa, *Acta Neurol. Scand.* 73, 449 (1986).



Crystals from ethyl acetate, mp 189-190° (Cook). Also reported as crystals from 2-propanol, mp 186-188° (Hrebabecky, Beranek); needles from methanol + ethyl acetate, mp 192-193° (Kiss). pKa 7.4. $[\alpha]_D^{25}$ +18.4° (c = 0.419 in water). uv max (in methanol): 268-269 nm (ε 8550). LD_{50} (14 day) in mice or rats (mg/kg): > 1000 i.v.: > 2000 s.c.; in male, female mice, male, female rats (mg/kg): > 5000, > 5000, 3471, 3390 orally (Shimizu).

THERAP CAT: Antineoplastic.

3494. Doxofylline. *7-(1,3-Dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione; 7-(1,3-dioxolan-2-ylmethyl)theophylline;* 2-(7'-theophyllinemethyl)-1,3-dioxolane; doxophylline; dioxyfilline; ABC-12/3; Ansimar; Maxivent; Ventax. $C_{11}H_{14}N_4O_4$; mol wt 266.26. C 49.62%, H 5.30%, N 21.04%, O 24.04%. Prepn: U. Avico *et al., Farmaco Ed. Sci.* 17, 73 (1962). Use as bronchodilator: Belg. pat. 868,556; J. S. Franzone, T. Tamietto, U.S. pat. 4,187,308 (1978, 1980 to Istituto Biologico Chemioterapico ABC). Pharmacology: J. S. Franzone *et al., Farmaco Ed. Sci.* 36, 201 (1981). Pharmacodynamics and toxicity in rats: J. S. Franzone *et al., ibid.* 220. HPLC determn in pharmaceutical compositions: C. Badini *et al., Farmaco Ed. Prat.* 37, 320 (1982). Clinical trial in obstructive pneumopathy: C. Bucca *et al., Int. J. Clin. Pharm. Res.* 11, Suppl 1, 101 (1982).

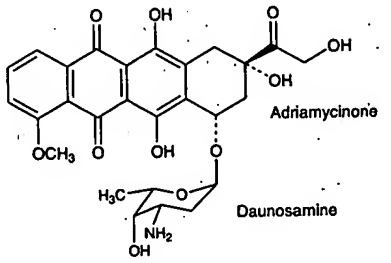


Crystals, mp 144-145.5°. Sol in water, acetone, ethyl acetate, benzene, chloroform, dioxane, hot methanol or hot ethanol. Practically insol in ethyl ether or petr ether. LD_{50} in mice (mg/kg): 841 orally; 215.6 i.v.; in rats: 1022.4 orally, 445 i.p. (Franzone).

THERAP CAT: Bronchodilator.

3495. Doxorubicin. *(8S-cis)-10-[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione;* 14-hydroxydaunomycin; NSC-123127; FI-106. $C_{27}H_{29}NO_{11}$; mol wt 543.53. C 59.67%, H 5.38%, N 2.58%, O 32.38%. Anthracycline antibiotic isolated from *Streptomyces peucetius* var *caesius:* F. Arcamone *et al.*, S. Afr. pat. 68 02378 and U.S. pat. 3,590,028 (1968 and 1971 to Farmitalia); *eidem, Biotechnol. Bioeng.* 11, 1101 (1969). Synthesis of derivs: F. Arcamone *et al.*, Ger. pat. 1,917,874 (1969 to Farmitalia), *C.A.* 73, 45799r (1970). Structural studies: F. Arcamone *et al., Tetrahedron Letters* 1969, 1007. Synthesis from daunomycin, *q.v.*: *eidem, Chim. Ind. (Milan)* 51, 834

(1969); *see also:* E. M. Acton *et al., J. Med. Chem.* **17**, 659 (1974); from 7-deoxydaunomycinone: T. H. Smith *et al.*, U.S. pat. 4,012,448 (1977 to Stanford Res. Inst.). Biochemical comparison with daunomycin: Wang *et al., Proc. Am. Assoc. Cancer Res.* **12**, No. 62, 77 (1971). In acid environment doxorubicin breaks up into a water-insol aglycone, *adriamycinone* ($C_{21}H_{18}O_9$), and a water-sol basic, reducing aminosugar, *daunosamine* ($C_6H_{13}NO_3$), 3-amino-2,3,6-trideoxy-L-lyxohexose: A. Di Marco *et al., Cancer Chemother. Rep.* (part 1) **53**, 33 (1969). Total synthesis of adriamycinone: F. Suzuki *et al., J. Am. Chem. Soc.* **100**, 2272 (1978); regiospecific synthesis: J. S. Swenton, P. W. Reynolds, *ibid.* 6188; of daunosamine: P. M. Wovkulich, M. R. Uskonovic, *Tetrahedron* **41**, 3455 (1985). Pharmacokinetic and chemotherapeutic studies: E. Arena *et al., Arzneimittel-Forsch.* **21**, 1258 (1971). Purification: E. Oppici *et al.*, Belg. pat. 898,506; *eidem*, Brit. pat. Appl. 2,133,005 (both 1984 to Farmitalia). As modulator of immune response in mice: E. Mihich, M. J. Ehrke, *Transplant. Proc.* **16**, 499 (1984). Doxorubicin's cytotoxicity appears to be due to its ability to intercalate with DNA, interact with plasma membranes and take part in oxidation-reduction reactions: T. R. Tritton, G. Yee, *Science* **217**, 248 (1982); H. Simpkins *et al., Cancer Res.* **44**, 613 (1984); R. S. Youngman, E. F. Elstner, *Arch. Biochem. Biophys.* **231**, 424 (1984). In treatment of cancer of the bladder: M. Pavone-Macaluso *et al., Urology* **23**, 40 (1984); breast: D. C. Tormey *et al., Am. J. Clin. Oncol.* **7**, 231 (1984); prostate: H. Scher *et al., J. Urol.* **131**, 1099 (1984). Toxicology: C. Bertazzoli *et al., Experientia* **26**, 389 (1970); *eidem, Toxicol. Appl. Pharmacol.* **21**, 287 (1972); R. D. Olson *et al., Life Sci.* **29**, 1393 (1981). Review of properties, biosynthesis, fermentation: R. J. White, R. M. Stroshane, *Drugs Pharm. Sci.* **22**, 569-594 (1984); of efficacy: H. L. Davis, T. E. Davis, *Cancer Treat. Rep.* **63**, 809-815 (1979). *Review:* R. H. Blum, S. K. Carter, *Ann. Int. Med.* **80**, 249-259 (1974); G. Aubel-Sadron, D. Londos-Gagliardi, *Biochimie* **66**, 333-352 (1984). Comprehensive description: A. Vigevani, M. J. Williamson, *Anal. Profiles Drug Subs.* **9**, 245-274 (1980). Book: *Doxorubicin*, F. Arcamone, Ed. (Academic Press, New York, 1981) 354 pp.



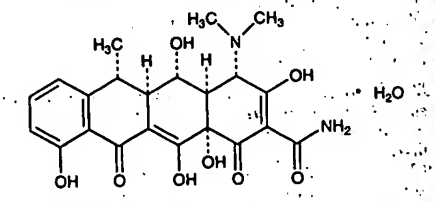
mp 229-231°.

Hydrochloride, $C_{27}H_{29}NO_{11}$·HCl, *Adriacin, Adriblastina, Adriamycin.* Orange-red colored thin needles, mp 204-205° (dec). $[\alpha]_D^{20}$ +248° (c = 0.1 in methanol). Absorption/uv max (methanol): 233, 252, 288, 479, 496, 529 nm. Sol in water, methanol, aq alcohols. Practically insol in acetone, benzene, chloroform, ethyl ether and petroleum ether. Aq solns are yellow-orange at acid pHs, orange-red at neutral pHs and violet-blue at pH > 9. Aq soln unchanged after one month at 5°, but unstable at higher temperatures or at either acid or alkaline pHs. LD_{50} i.v. in mice: 21.1 mg/kg (Bertazzoli, 1970).

Note: Doxorubicin may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 86.

THERAP CAT: Antineoplastic.

3496. Doxycycline. *[4S-(4α,4aα,5α,5aα,6α,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate;* α-6-deoxy-5-hydroxytetracycline monohydrate; α-6-deoxyoxytetracycline monohydrate; 5-hydroxy-α-6-deoxytetracycline monohydrate; GS-3065; Jenacyclin; Supracyclin; Vibramycin. $C_{22}H_{24}N_2O_8.H_2O$; mol wt 462.46. C 57.14%, H 5.67%, N 6.06%, O 31.14%. Prepn of family of 6-deoxytetracyclines: C. R. Stephens *et al., J. Am. Chem. Soc.* **80**, 5324 (1958). *See also:* McCormick, Jens U.S. pat. 3,019,260 (1962 to Am. Cyanamid). Prep separation and configuration of 6α- and 6β-epimers: M von Wittenau *et al., J. Am. Chem. Soc.* **84**, 2645 (1962); C R. Stephens *et al., ibid.* **85**, 2643 (1963). Prepn of deoxyoxytetracycline: R. K. Blackwood *et al.*, U.S. p 3,200,149 (1965 to Pfizer). ^{1}H-NMR study: M. S. Wittenau, R. K. Blackwood, *J. Org. Chem.* **31**, 613 (196 Biological properties: English, *Proc. Soc. Exp. Biol. M* **122**, 1107 (1966). Pharmacology: Fabre, *Chemothera* **11**, 73 (1966); Gibaldi, *ibid.* **12**, 265 (1967). Toxicity hyclate: Goldenthal, *Toxicol. Appl. Pharmacol.* **18**, (1971). Clinical trial in prophylaxis of leptospirosis: E Takafuji *et al., N. Engl. J. Med.* **310**, 497 (1984). *Review:* Edwards in *Pharmacological and Biochemical Properties Drug Substances* vol. 2, M. E. Goldberg, Ed. (Am: Phar Assoc., Washington, DC, 1979) pp 305-332.



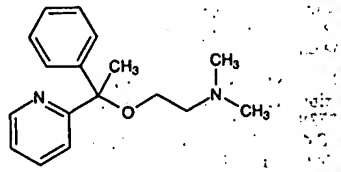
Hydrochloride hemiethanolate hemihydrate, $C_{22}H_{24}Cl$ $N_2O_8.\frac{1}{2}C_2H_6O.\frac{1}{2}H_2O$, *doxycycline hyclate, Azudoxat, Ba sado, Clinofug, Diocimex, Doryx, Doxatet, Doxicrisol, Dox chel hyclate, Doxylar, Doxytem, Duradoxal, Granudoxy, H dramycin, Mespafin, Nordox, Paldomycin, Retens, Ronaxa Sigadoxin, Spanor, Tetradox, Unacil, Vibramycin Hyclate Vibra-Tabs, Vibraveineuse, Vibravenös, Zadorin.* Ligh yellow, crystalline powder from ethanol + HCl. Char without melting at about 201°. $[\alpha]_D^{25}$ −110° (c = 1 in 0.01 methanolic HCl). uv max (0.01*N* methanolic HCl): 26 351 nm (log ε 4.24, 4.12). Sol in water. The alcohol and water of crystallization are lost by drying at 100° under reduced pressure. More active biologically than the corresponding 6β-epimer hydrochloride (Wittenau, 1962). LD_{50} i.p. in rats: 262 mg/kg (Goldenthal).

Sodium metaphosphate (3:1), $3(C_{22}H_{24}N_2O_8).NaPO_3$ $(HPO_3)_3$, *doxycycline fosfatex, Sigacyclat.*

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

3497. Doxylamine. *N,N-Dimethyl-2-[1-phenyl-1-(2-py idinyl)ethoxy]ethanamine; 2-[α-(2-dimethylaminoethoxy)-α methylbenzyl]pyridine;* phenyl-2-pyridylmethyl-β-*N,N*-di methylaminoethyl ether; 2-dimethylaminoethoxyphenyl methyl-2-picoline. $C_{17}H_{22}N_2O$; mol wt 270.37. C 75.52% H 8.20%, N 10.36%, O 5.92%. Prepd from phenyl-2-pyridylmethylcarbinol and β-*N,N*-dimethylaminoethyl chloride in the presence of sodamide in xylene: Sperber *et al., J. Am. Chem. Soc.* **71**, 887 (1949). GC determn: H. C. Thompson *et al., J. Chromatog. Sci.* **20**, 373 (1982). Pharmacology, antihistaminic activity: B. B. Brown, H. Werner, *J. Lab Clin. Med.* **33**, 325 (1948). Hypnotic efficacy: F. Sjöqvist, L. Lasagna, *Clin. Pharmacol. Ther.* **8**, 48 (1967). Chronic toxicity study of the succinate: C. D. Jackson, B. Blackwell, *J. Am. Coll. Toxicol.* **12**, 1 (1993). *Review:* T. J. Haley, *Dangerous Prop. Ind. Mater. Rep.* **2**, 17 (1982).



Liquid, $bp_{0.5}$ 137-141°. Sol in acids. Slightly volatile, darkens on exposure to light.

Succinate, $C_{17}H_{22}N_2O.C_4H_6O_4$, *Mereprine, Alsadorm, Dr capryn succinate, Gittalun, Hoggar N, Sedaplus, Unison* Crystals, mp 100-104°, sol in water. One gram dissolves